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Helsinki 30.12.2003

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Patenttihakemus nro Patent application no	**20022007**
Tekemispäivä Filing date	**08.11.2002**
Kansainvälinen luokka International class	**A61K**

Keksinnön nimitys
Title of invention

"Oromucosal formulation and process for preparing the same"
(Oromukosaalinen valmiste ja menetelmä sen valmistamiseksi)

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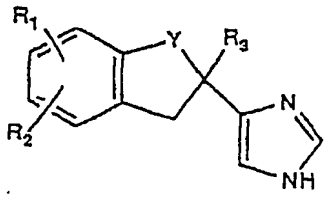
OROMUCOSAL FORMULATION AND PROCESS FOR PREPARING THE SAME

FIELD OF THE INVENTION

The present invention relates to an oromucosal formulation comprising as an active ingredient a substituted imidazole derivative of formula (I)



(I)

wherein Y is $-CH_2-$ or -CO-, R_1 is halo or hydroxy, R_2 is H or halo and R_3 is H or lower alkyl, or an acid addition salt thereof.

The invention also relates to a process for preparing the oromucosal formulation in question.

BACKGROUND OF THE INVENTION

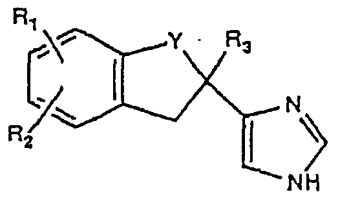
The compounds of the above-mentioned formula (I) are highly selective and long-acting antagonists of α_2-adrenoceptors. The compounds are especially valuable in the treatment of cognitive disorders. Compounds of formula (I) and their preparation have been described in patent publication EP 0 618 906 B1. Specific examples of such compounds are 4-(2-ethyl-5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole and 4-(5-fluoro-2,3-dihydro-1-inden-2-yl)-1H-imidazole.

Although the compounds of formula (I) and their salts have good properties as such, they have disadvantages, when formulated for conventional oral administration, i.e. the normal route for administering said compounds. The problem is that the compounds rather quickly decompose in the gastrointestinal area. This in turn significantly lowers the effect of the compounds in question.

It has now been found that the above-mentioned problem can be avoided by formulating the compounds of formula (I) into oromucosal formulations. Such formulations are effective and easy to handle, and therefore they have an advantage in terms of practical administration by the patient.

SUMMARY OF THE INVENTION

The present invention relates to an oromucosal formulation comprising as an active ingredient a substituted imidazole derivative of formula (I)



(I)

where Y is $-CH_2-$ or $-CO-$, R_1 is halo or hydroxy, R_2 is H or halo and R_3 is H or lower alkyl, or an acid addition salt thereof, together with additives conventionally used in oromucosal formulations.

The invention also relates to a process for preparing an oromucosal formulation described above.

DETAILED DESCRIPTION OF THE INVENTION

Suitable additives to be used in the formulation according to the present invention are adjuvants, expedients etc. including solvents, preserving agents, flavouring agents and fillers. Preferred solvents are alcohols, especially ethanol, water and mixtures thereof. Preferred preserving agents are lower alkyl parahydroxybenzoates, especially methyl and propyl parahydroxybenzoate, and mixtures thereof. Preferred flavouring agents are aspartame, artificial flavours, such as black currant 502.009, and mixtures thereof.

In this context, the oromucosal formulation means any type of formulation administered via oral mucosa. Such formulations include e.g. sprays, gels, buccal tablets and pastes, sublingual tablets and like. The formulation is preferably in the form of a spray.

An especially preferred active ingredient is fipamezole (JP-1730, 4-(2-ethyl-5-fluoro-indan-2yl)-1H-imidazole hydrochloride). A formulation containing said preferred active ingredient is prepared according to the invention by mixing and dissolving ethanol (96%), purified water, methylparahydroxybenzoate, propylparahydroxybenzoate and aspartame at room temperature, at +15-+25 °C. Followed by adding and dissolving 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole and artificial flavour, such as black currant 502.009A, at room tem-

perature, at +15-+25 °C. The volume of the mixture is adjusted with purified water, followed by filtering and the desired spray formulation is recovered.

The following examples illustrate the invention, but are not intended to restrict the scope of the invention.

Example 1

Spray formulation containing 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole hydrochloride (fipamezole)

Fipamezole oromucosal spray

Ingredient	Quantity per 1 ml	Function
Fipamezole	15.0 mg	Active
Methyl parahydroxybenzoate	1.8 mg	Preservative
Propyl parahydroxybenzoate	0.2 mg	Preservative
Aspartame	0.5 mg	Flavouring agent
Artificial flavour*	0.4 mg	Flavouring agent
Ethanol (96 %)	0.416 ml	Solvent
Purified water	ad 1.0 ml	Solvent

*Artificial flavour, such as black currant 502.009A, for example, but not restricted to.

Example 2

Spray formulation containing 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole hydrochloride (fipamezole)

Fipamezole oromucosal spray

Ingredient	Quantity per 1 ml	Function
Fipamezole	161.0 mg	Active
Methyl parahydroxybenzoate	1.8 mg	Preservative
Propyl parahydroxybenzoate	0.2 mg	Preservative
Aspartame	0.5 mg	Flavouring agent
Artificial flavour*	0.4 mg	Flavouring agent

Ethanol (96 %)	0.416 ml	Solvent
Purified water	ad 1.0 ml	Solvent

*Artificial flavour, such as black currant 502.009A, for example, but not restricted to.

Example 3

Preparation of a spray formulation containing 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole hydrochloride (fipamezole)

416.0 ml of ethanol (96%) was mixed with 450.0 ml of purified water to form a homogenous mixture. 1.80 g of methylparahydroxybenzoate, 0.20 g of propylparahydroxybenzoate and 0.5 g of aspartame were added to the mixture and dissolved at room temperature, at +15-+25 °C. 15.0 g of fipamezole, 0.4 g of black currant flavour were added to the mixture and dissolved at room temperature, at +15-+25 °C. The volume of the mixture was adjusted to 1000.0 ml with purified water. The solution was filtered and the desired spray formulation was recovered.

Example 4.

Preparation of an oromucosal gel formulation containing 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole hydrochloride (fipamezole) 30 mg

Composition

	Ingredient	**Amount/single dose**
1	Fipamezole	30 mg
2	Ethanol (96 %)	250 mg
3	Poloxamer 407	200 mg
4	Liquid flavour (artificial)	0.5 mg
5	Aspartame (sweetener)	0.5 mg
6	Purified water	519 mg
	Total of	1000 mg

Method of preparation

Fipamezole (1) and ethanol (96 %) (2) are mixed and dissolved to form a solution A. Purified water (6), poloxamer 407 (3), liquid flavour (4), and aspartame (5) are mixed and dissolved to form a solution B. Solution A and solution B are cooled down to approx. +5 °C, and mixed together to form a homogenous solution. Oromucosal gel formulation is recovered.

Example 5.

Preparation of a mucoadhesive buccal tablet formulation containing 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole hydrochloride (fipamezole) 30 mg

Composition

Ingredient		Amount/single dose
1	Fipamezole	30 mg
2	Carbomer 934P	12.35 mg
3	Hydroxypropylmethylcellulose	49.4 mg
4	Flavour (artificial)	4 mg
5	Aspartame (sweetener)	4 mg
6	Magnesium stearate	0.25 mg
	Total of	100 mg

Method of preparation

Fipamezole (1), carbomer 934P (2), hydroxypropylmethylcellulose (3), flavour (4), aspartame (5), and magnesium stearate (6) are mixed to form a homogenous mixture. The mixture is compressed to tablets of a suitable size. Mucoadhesive buccal tablets are recovered.

Example 6.

Preparation of a sublingual tablet formulation containing 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole hydrochloride (fipamezole) 30 mg

Composition

	Ingredient	Amount/single dose
1	Fipamezole	30 mg
2	Lactose monohydrate	30 mg
3	Povidone	2.4 mg
4	Microcrystalline cellulose	10.8 mg
5	Flavour	3.2 mg
6	Aspartame (sweetener)	3.2 mg
7	Magnesium stearate	0.4 mg
	Total of	80 mg

Method of preparation

Fipamezole (1), lactose monohydrate (2), flavour (5), and aspartame (6) are mixed to form a homogenous mixture. The mixture is granulated with 10 % aqueous solution of povidone (3). Granules are formed in either high-shear or low-shear mixer. Granulated mixture is let to dry. Dry, granulated mixture is passed through a screen to obtain freely flowing granulate. Microcrystalline cellulose (4) and magnesium stearate (7) are mixed with the granulate. The final blend is compressed to tablets of a suitable size. Sublingual tablets are recovered.

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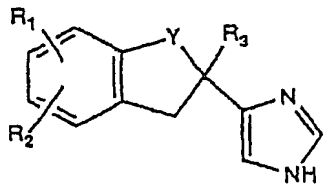
Claims

1. An oromucosal formulation comprising as an active ingredient a substituted imidazole derivative of formula (I)



(I)

where Y is $-CH_2-$ or $-CO-$, R_1 is halo or hydroxy, R_2 is H or halo and R_3 is H or lower alkyl, or an acid addition salt thereof, together with additives conventionally used in oromucosal formulations.

2. A formulation according to claim 1 wherein the active ingredient is 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole or its acid salt, such as hydrochloride.

3. A formulation according to claim 1 or 2 wherein the additives are selected from solvents, preserving agents, flavouring agents and mixtures thereof.

4. A formulation according to claim 3 wherein the solvent is selected from ethanol, water and a mixture thereof.

5. A formulation according to claim 3 or 4 wherein the preserving agent is selected from methyl parahydroxybenzoate, propyl parahydroxybenzoate and a mixture thereof.

6. A formulation according to any of claims 3 to 5 wherein the flavouring agent is selected from aspartame, black currant and a mixture thereof.

7. A formulation according to claim 1 comprising the following components: (a) 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole or its acid salt, such as hydrochloride, (b) ethanol and water, (c) methyl parahydroxybenzoate and propyl parahydroxybenzoate, and (d) aspartame and black currant.

8. A formulation according to any of the preceding claims wherein the formulation is in the form of a spray, gel, a mucoadhesive buccal tablet or paste, or a sublingual tablet.

9. A formulation according to claim 8 wherein the formulation is in the form of a spray.

10. A process for preparing a formulation according to claim 7 comprising mixing and dissolving ethanol (96%), purified water, methyl parahydroxybenzoate, propyl parahydroxybenzoate and aspartame at room temperature, at +15-+25 °C; followed by adding and dissolving 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole hydrochloride and artificial flavour, such as black currant 502.009A, at room temperature, at +15-+25 °C; adjusting the volume of the mixture with purified water, followed by filtering and recovering the desired spray formulation.

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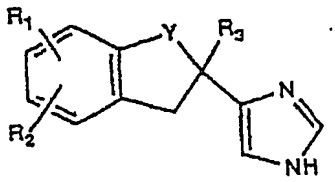
(57) Abstract

An oromucosal formulation comprising as an active ingredient a substituted imidazole derivative of formula (I)

(I)



where Y is $-CH_2-$ or $-CO-$, R_1 is halo or hydroxy, R_2 is H or halo and R_3 is H or lower alkyl, or an acid addition salt thereof, together with additives conventionally used in oromucosal formulations, and a process for its preparation.